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Cell-Mediated Immunity and Its Role in Resistance to Infection

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The recently acquired knowledge of the importance of cell-mediated immunity in many illnesses and the discovery of a variety of substances that can restore certain cell-mediated immune functions has served to focus the attention of physicians on this area of immunity. It is important for practicing physicians to have a clear understanding of current knowledge of the role of cell-mediated immunity in resistance to infection and how this arm of the immune system relates to the diagnosis and therapy of infectious diseases.

RECENT ADVANCES in treatment of patients with malignancies, collagen-vascular disorders and organ transplants have been accompanied by discouragingly high rates of infection. The defects in host defense which are frequently associated with these conditions, along with the profound immunologic abnormalities which result from the administration of newer immunosuppressive therapeutic regimens, have resulted in an increase in susceptibility to life-threatening infections in these patients—infections caused by a variety of opportunistic organisms. Great effort has been expended in studying persons with normal and compromised immunologic functions in order to discover means whereby immunologic defects might be prevented or overcome so as to lessen the frequency of infection.

While it was suspected for years that a form of immunity mediated by cells was important in defense against certain infections, this hypothesis was not proven until Chase, in a series of classic experiments in guinea pigs, showed that lymphoid cells could successfully transfer cutaneous delayed hypersensitivity to tubercle bacilli from one animal to another.[1] Cutaneous delayed hypersensitivity (DH) is an inflammatory response that reflects the ability of the host's cellular immune system to respond to the eliciting antigen (organism). In more recent experiments, it has been shown that the lymphoid cells that are able to transfer protection against certain infectious agents are thymus-derived or T lymphocytes[2] (in contrast to B lymphocytes which are the cells responsible for antibody production). For example, thoracic duct lymphocytes transferred from animals immunized to Mycobacterium tuberculosis into unimmunized animals have been shown to confer protection to tuberculosis.[3] These experiments have allowed for a working definition of cell-mediated immunity (CMI) as that particular response of the immune system which requires previously sensitized thymus-derived lymphocytes and is independent of

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ABBREVIATIONS USED IN TEXT

BCG = bacille Calmette Guérin
CMI = cell-mediated immunity
Con A = concanavalin A
DH = delayed hypersensitivity
LCM = lymphocytic choriomeningitis virus
MIF = migration inhibition factor
PHA = phytohemagglutinin
SKSD = streptokinase-streptodornase

circulating antibody. CMI has been found to be of major importance in resistance to a variety of facultative and obligate intracellular organisms (many of which persist and multiply within phagocytic cells of the reticuloendothelial system). Many of these organisms are opportunistic pathogens that infect immunocompromised hosts (Table 1). A role for CMI has also been elucidated in other important biologic processes such as rejection of allografts, resistance to tumor and graft-versus-host reactions. These will not be considered here.

CMI and humoral immunity may be operative, either together or singly, against any particular pathogen. Humoral antibody plays a major role in resistance against a number of microorganisms and their toxins, including such bacteria as Group A streptococci and Hemophilus influenzae, viruses such as influenza virus and poliovirus, and toxins from bacteria such as Corynebacterium diphtheriae and Clostridium tetani. Humoral immunity and CMI differ in many respects, and a number of these differences are given in Table 2.

In addition to specific antibody and CMI, a variety of nonspecific mechanisms such as the complement cascade and polymorphonuclear leukocytes have important roles in resistance to infection, but will not be considered here. This will not be a complete review but will focus on the mechanisms of CMI, the deficiencies in the functioning of CMI, and diagnostic and therapeutic implications.

Mechanisms of Cell-Mediated Immunity

The cell-mediated immune response to an organism is initiated when T lymphocytes are specifically sensitized by contact with its foreign antigens (afferent limb) (Figure 1). Contact between lymphocytes and antigen occurs either at the site of infection or in lymph nodes draining the peripheral area where the organism has invaded. In lymph nodes, T lymphocytes localize to and are sensitized in periarteriolar areas which are referred to as thymus-dependent areas. Two types of antigen stimulate T lymphocytes but not B lymphocytes: the first is certain small molecules such as arsenobenzoate-N-acetyl tyrosine or some synthetic peptide copolymers of tyrosine or glutamic acid; the second is larger molecules, only part of which are recognized as foreign, such as dinitrochlorobenzene complexed with skin protein.[4] Those antigens most likely to induce sensitization of T lymphocytes *in vivo* are proteins found on the membranes of living cells. Antigens on dead cells or antigens alone are less effective.

Macrophages, bone marrow-derived tissue

TABLE 1.—*Pathogens Against Which Cell-Mediated Immunity Appears to Be Important in Host Defense.*

Bacteria	*Viruses*	*Fungi*	*Protozoa*	*Helminths*	*Unclassified*
Mycobacteria, including M. tuberculosis and M. leprae	Herpes simplex	Aspergillus species	Toxoplasma gondii	Schistosome species	Pneumocystis carinii
Salmonella species	Herpes zoster	Candida species	Plasmodia species	? Strongyloides stercorales	
Listeria monocytogenes	Cytomegalovirus	Cryptococcus neoformans			
Francisella tularensis (Tularemia)	Rubeola (measles)	Phycomycetes species			
Brucella species	Vaccinia	Histoplasma capsulatum			
Treponema pallidum		Coccidioides immitis			
Malleomyces pseudomallei (Meliodosis)					
Malleomyces mallei (Glanders)					

TABLE 2.—*General Characteristics of Humoral and Cellular Immunity*

Characteristic	*Humoral Immunity*	*Cellular Immunity*
Time course for maximal effect	Minutes to hours	Usually days
Mediator cell	B lymphocytes and derived plasma cells	T lymphocytes
Effector	Antibody	Lymphocytes and macrophages
Active against	Extracellular pathogens	Intracellular pathogens

phagocytes, appear to play an early role in processing of antigens. In certain situations, antigens phagocytosed and then processed by macrophages and subsequently presented to T lymphocytes are more effective sensitizers of CMI than are the antigens alone. There is evidence that modification of antigens by a variety of means including processing by macrophages,[4] enzymatic degradation[5] and chemical alteration[6] changes antigens in such a way as to make them more immunogenic.

Within one or two days after exposure of T lymphocytes to antigen modified by macrophages or to antigen alone, a proportion of the exposed T lymphocytes undergoes a process known as transformation (Figure 2). This process produces specifically immune cells which are then able to mediate the functions of CMI *in vivo* and *in vitro.* These cells will be referred to as sensitized lymphocytes. The lymphocytes which transform enlarge, the nuclear material changes from heterochromatin to euchromatin, synthesis of ribonucleic acid (RNA), deoxyribonucleic acid (DNA) and protein increases, and the cells eventually undergo multiple divisions. Lymphocyte transformation may be monitored *in vitro* and *in vivo* by both morphologic changes and by quantitative demonstration of DNA synthesis (incorporation of radiotagged precursors of DNA). *In vitro,* T lymphocyte transformation may be induced not only by specific antigen but also by mitogens, such as concanavalin A (Con A) and phytohemagglutinin (PHA), which are lectins that bind to carbohydrates of cell membranes. *In vitro* lymphocyte transformation as a measure of CMI correlates with DH skin responses (such as to tuberculin or histoplasmin).

Once sensitized to antigen, T lymphocytes become the mediators of the effector limb of CMI (efferent limb), or may become long-lived "memory cells" (Figure 3). The "memory" T lymphocytes circulate in blood and lymphatics (T lymphocytes make up approximately 60 percent of circulating blood lymphocytes[7]) and are specifically committed—that is, they will respond only to that particular antigen to which they were previously exposed. They are responsible for the

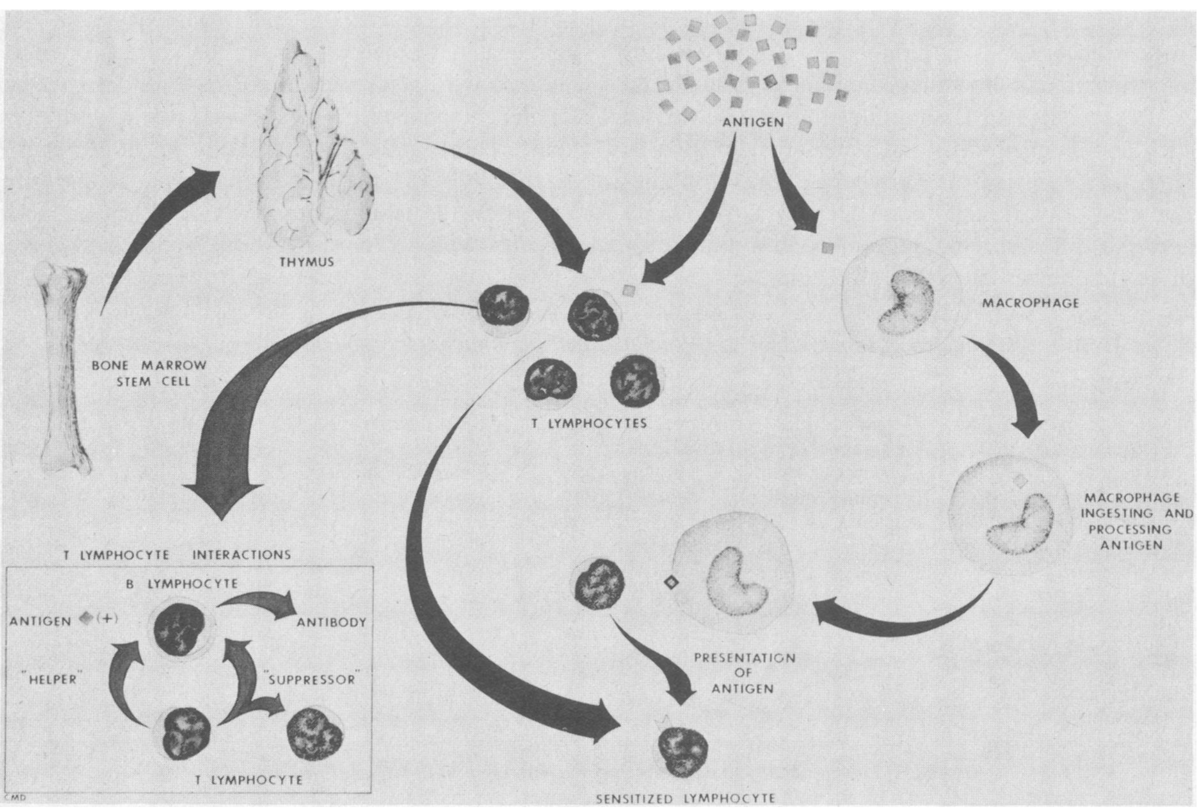

Figure 1.—Cell-Mediated Immunity—Afferent Limb. T lymphocytes are derived from bone marrow stem cells and are converted to T lymphocytes in the thymus gland. When exposed either directly to antigen or to antigen processed by macrophages, a proportion of T lymphocytes becomes sensitized—that is, have the potential to activate the efferent limb of cell-mediated immunity when reexposed to antigen (Figure 3). T lymphocytes may also regulate B lymphocyte production of antibody and may regulate the response of other T lymphocytes (insert).

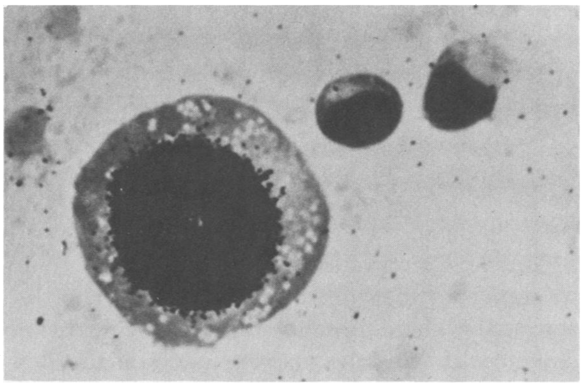

Figure 2.—Blast Transformation of Lymphocytes. Two resting human lymphocytes (right) are next to a lymphocyte stimulated by streptokinase-streptodornase undergoing blast transformation. The cells were pulsed with a radioactive precursor of DNA (^{3}H-labeled thymidine) and autoradiography was carried out. The nucleus of the transforming cell took up the ^{3}H-thymidine because of the rapid rate of DNA synthesis and appears blackened by the effect of the radioactivity on the emulsion. (X400)

heightened rapid response of CMI upon reexposure to the original sensitizing antigen.

After reexposure to an infectious agent (antigen), specifically sensitized T lymphocytes may function in several ways to protect the host. They may produce a variety of soluble substances referred to as lymphokines which can stimulate lymphocytes and phagocytic cells to establish an effective host defense. Most of these lymphokines and their functions have been shown *in vitro* only. Several of them are listed in Table 3. A blastogenic factor is one such product of sensitized lymphocytes exposed to antigen at a peripheral site. When released into the local area or into the systemic circulation, it may enhance transformation in other lymphocytes, thereby enhancing the overall immune response. Other lymphokines attract macrophages to the site of antigen (infection), inhibit macrophage migration from that site and activate the macrophages (Figure 3). In

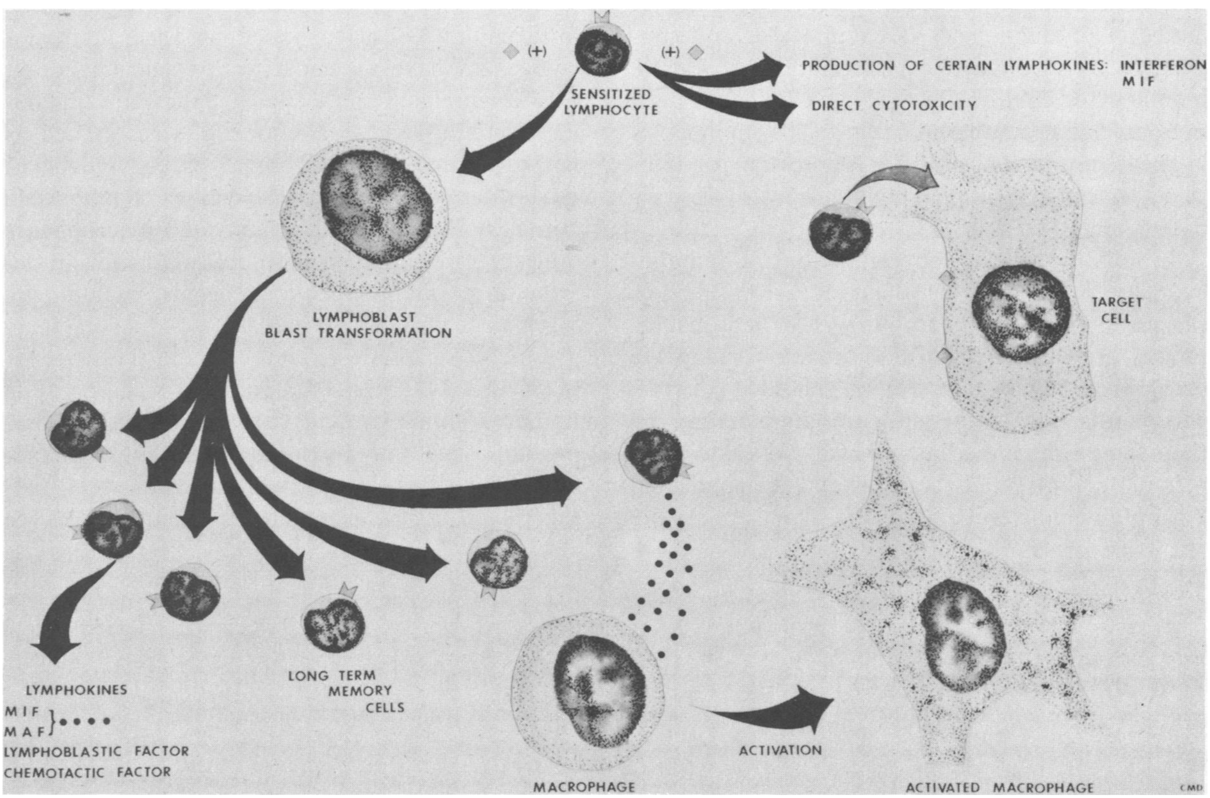

Figure 3.—Cell-Mediated Immunity—Efferent Limb. Sensitized T lymphocytes reexposed to the sensitizing antigen may undergo blast transformation and then proliferate. The subsequent progeny of sensitized lymphocytes may produce a variety of lymphokines which mediate the cellular inflammatory response. These lymphokines include migration inhibition factor (MIF) and aggregation factor (MAF) which may activate macrophages, chemotactic factor which attracts monocytes and macrophages, and lymphoblastic factor which stimulates other lymphocytes to undergo transformation. Some of these T lymphocytes may become long-term "memory" cells which circulate in blood and lymph and which remain sensitized for years. Sensitized T lymphocytes exposed to the appropriate antigen may also produce certain lymphokines (for example, MIF or interferon) without undergoing transformation or proliferation. These nontransforming cells may lyse target cells that have an appropriate antigen on their cell surface (such as viral).

this manner, major cell types necessary for effective resistance are mobilized and activated to destroy or at least contain the pathogen at the site of invasion. Examples of containment are the granulomas which form about tubercle bacilli, schistosome eggs and histoplasma. Interestingly, the production of many of these lymphokines, including interferon, is not necessarily correlated with blast transformation and some—such as migration inhibition factor (MIF)—may be produced by B lymphocytes as well as T lymphocytes.[8,9] T lymphocytes may also directly lyse host cells which are infected (for example, viral infected cells with viral antigen on their surfaces), thereby destroying the intracellular environment necessary for replication of the microorganism. Unsensitized lymphocytes in the presence of antivirus antibody have been shown to lyse these virus-infected cells as well.

T lymphocytes may have numerous other functions, including enhancement or suppression of antibody production by B lymphocytes and suppression of lymphocyte transformation by other T lymphocytes *in vitro*. Recently, evidence has been presented that a subpopulation of T lymphocytes is the factor responsible for depression of lymphocyte transformation in patients with disseminated fungal disease.[10]

In addition to the above functions, T lymphocytes are responsible for changing normal macrophages to activated macrophages. Normal macrophages are derived from bone marrow monocyte precursors which migrate via blood to tissue. Morphologically, these cells are characterized by their large size, spreading borders, abundant cytoplasmic granules and vacuoles, and their indented or multiple nuclei (Figure 4). They are motile and phagocytic and adhere to glass; they also have membrane receptors for certain subclasses of immunoglobulin G (IgG), immunoglobulin M (IgM) and complement. Normal macrophages ingest a variety of particulate materials, including pathogenic microorganisms, but their ability to kill these microorganisms varies considerably with the pathogen.

The activation of macrophages occurs through a specific immune process. Macrophages become activated when exposed to specifically sensitized lymphocytes plus the antigen to which the lymphocytes were previously sensitized or when exposed to certain substances such as bacterial endotoxin. These activated cells differ in certain respects from normal macrophages (Table 4) (Figure 4). The most important difference is their greatly increased capacity to inhibit or kill (efferent limb) intracellular pathogens. This effect appears to be nonspecific; thus, macrophages activated *in vivo* by lymphocytes exposed to one intracellular pathogen (such as Listeria monocytogenes) have the capacity to efficiently inhibit or kill unrelated intracellular pathogens, including bacteria such as Salmonella, viruses such as herpes simplex, fungi such as Cryptococcus neoformans and protozoa such as Toxoplasma gondii.[11] The presence of activated macrophages appears to be the most important factor in resistance to many infectious agents, including a number of those listed in Table 1.

Finally, as alluded to above, it has been recognized that synergistic interactions occur between humoral immunity and CMI. A particularly important aspect may be the enhancement of phagocytosis by macrophages which occurs when certain microorganisms such as Salmonella[11] are

TABLE 3.—*Some Products of Activated Lymphocytes*

Product	*Activity*
Affects lymphocytes	
Blastic factor	Induces normal lymphocytes to undergo blast transformation
Affects macrophages	
Migration inhibition factor (MIF)	Inhibits (and activates?) migration of macrophages
Aggregation factor (MAF)	Agglutinates macrophages
Chemotactic factor	Attracts macrophages and monocytes
Affects other cells	
Lymphotoxins	Lyse various cell lines in culture
Growth inhibitory factors	Prevent proliferation without damaging cells
Other	
Skin reaction factor	Causes indurated skin lesions
Interferon	Inhibits viral multiplication in cultured cells
Basophil and eosinophil chemotactic factor	Attracts basophils and eosinophils

coated with antibody. Although parasitized red blood cells may be destroyed by humoral factors or by macrophages from malaria-infected animals, antibody and macrophages together destroy malaria-infected red blood cells more quickly and more completely than either alone.[12] On the other hand, antagonism between humoral and cellular immunity has also been described[13,14]—for example, the DH skin response to a specific antigen may be blocked by antigen-antibody complexes in mice.

Evidence for the Role of CMI in Resistance to Infection

The most convincing evidence that CMI plays a major role in resistance to infection has come from experimental animal models of infections due to certain intracellular pathogens. Several examples of these are described in this section.

The classic model depicting the function of cellular immunity and its importance in bacterial disease is listeriosis in mice.[15,16] When a sublethal number of Listeria are injected intravenously into mice, the bacteria initially localize and multiply in the liver and spleen. After three days of logarithmic growth, the number of bacteria in these organs stabilizes and then decreases, and eventually the infection is eradicated. The mice are then resistant to an inoculum containing as many as 100 times the number of bacteria that cause death in 100 percent of mice. This remarkable resistance cannot be transferred with serum of immune mice but can be with their spleen cells. The appearance of specifically sensitized lymphocytes coincides with the appearance of DH to Listeria and with the eradication of bacteria from the tissues (Figure 5). Furthermore, nonimmune mice injected with sensitized lymphocytes from mice immune to Listeria—but not with lymphocytes from mice immune to other organisms, such as bacille Calmette Guérin (BCG)—are highly and specifically resistant to Listeria challenge. Previously committed T lymphocytes are the cells responsible for mediating the observed resistance and they do so by activating macrophages. Thus, both sensitized T lymphocytes and macrophages are necessary for proper functioning of resistance to Listeria. Macrophages obtained from the peritoneal cavities of animals infected two weeks earlier with Listeria have the properties of activated macrophages. Whereas Listeria are able to multiply in macrophages of normal mice, they are killed rapidly by macrophages of mice infected with Listeria. These activated macrophages have been shown to be present in the liver, spleen and peritoneal cavity at the time during the acute infection when the organisms are being eliminated from the liver and spleen (fourth day after infection). As discussed in the previous section, these activated macrophages in Listeria-infected animals have the capacity to inhibit or kill not only Listeria but a variety of other intracellular pathogens as well as to confer resistance *in vivo* to these unrelated

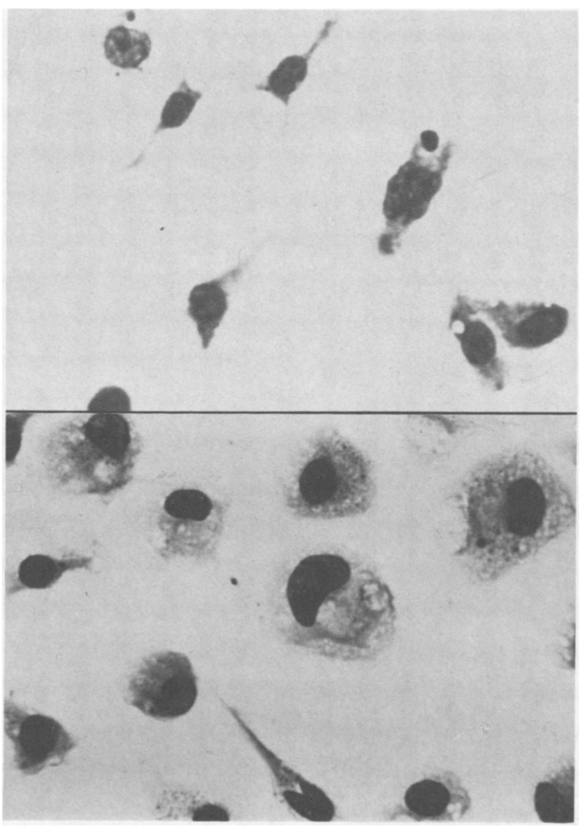

Figure 4.—Normal and Activated Macrophages. Upper, Normal macrophages are large mononuclear cells with cytoplasmic granules and vacuoles, indented or multiple nuclei, and spreading borders. **Lower,** Activated macrophages are larger, have more granules and vacuoles, spread more on glass, and have an increased capacity to kill microorganisms. (X160)

TABLE 4.—*Properties of Activated Macrophages*

Large size, more complex morphology
Increased spreading on glass; enhanced phagocytosis
Increased lysosomal hydrolase levels
Higher ratio of glucose metabolism by hexose monophosphate shunt as compared with glycolytic pathway
Increased digestive capacity, respiratory rate, and mitotic rate
Increased capacity to kill or inhibit replication of a variety of organisms

organisms. This ability of activated macrophages to kill completely unrelated organisms (such as protozoa and viruses) is why these cells are considered to represent the nonspecific effector arm of cellular immunity. This model, murine listeriosis, illustrates the essential role of CMI in resistance to intracellular bacterial infections in mammalian hosts as well as the interrelationships between the specific and nonspecific limb of cellular immunity (Figure 5).

It is important to realize that infection with intracellular bacteria may have at least three different outcomes depending on the infecting organisms and the response of the host. Macrophages may destroy all bacteria; the bacteria may be phagocytosed by macrophages but not be killed, resulting in dissemination and death of the host; or macrophages may not kill the pathogen, but they may limit multiplication and dissemination by granuloma formation (in tuberculosis, for example). To a large extent, therefore, resistance to intracellular bacteria depends on the presence of adequate numbers of activated macrophages that are able to kill or limit spread of the bacteria. As mentioned above, these findings are not unique to Listeria, but extend to many viruses, protozoa and fungi, as well as to other intracellular bacteria.

The important functional immune response to certain viral infections, particularly those in which

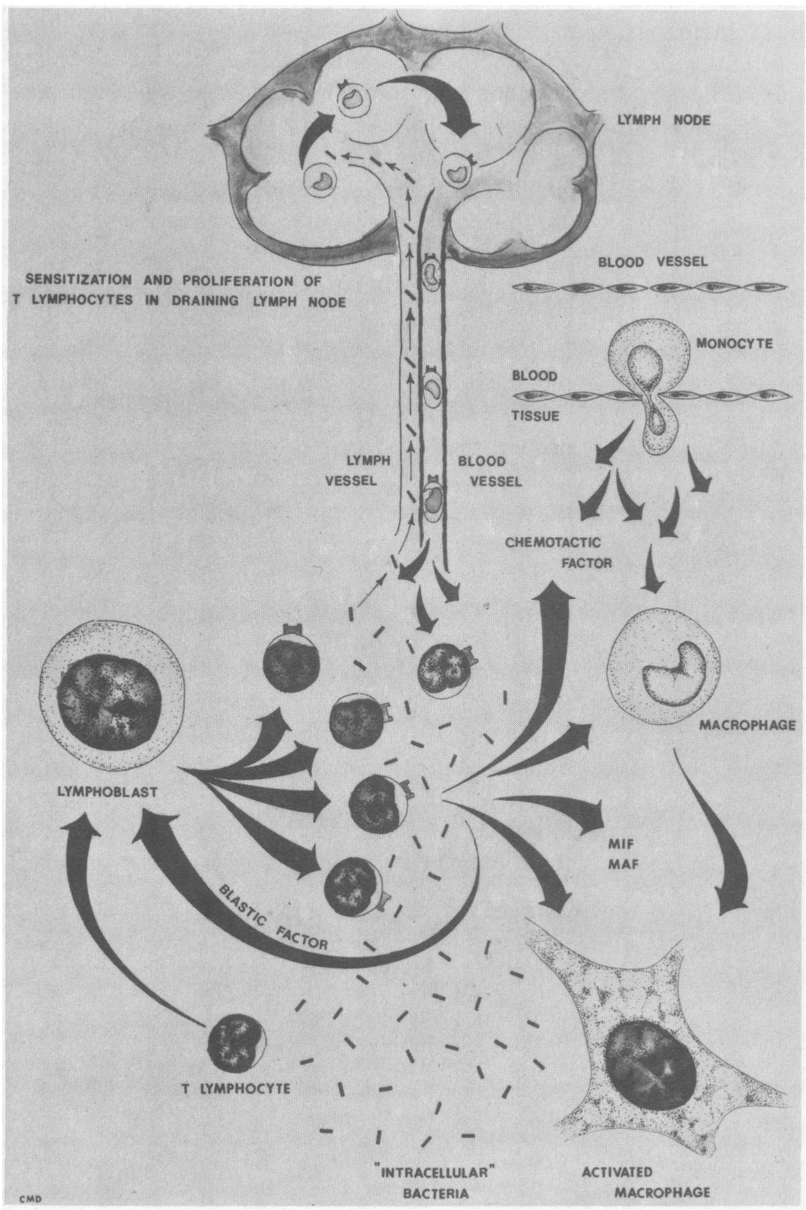

Figure 5.—Development of Resistance to Intracellular Bacteria. A proportion of lymphocytes in peripheral tissue exposed to intracellular bacteria undergo blast transformation and proliferation. Lymphocytes in draining lymph nodes may be exposed to antigens of the bacteria as well (via lymph channels) and undergo blast transformation and proliferation; they then return by the circulatory system to the site of antigen. Lymphocytes from both these sources produce lymphokines which attract other inflammatory cells (such as monocytes from blood). These lymphokines also serve to activate macrophages and induce other lymphocytes to undergo blast transformation. Activated macrophages ingest and kill the intracellular bacteria.

viral transmission occurs by cell to cell contact rather than by release of virus into the extracellular environment, appears to be cell-mediated.[17,18] For a particular virus, an individual function or a combination of functions of sensitized T lymphocytes may be important—such as (1) mobilization of macrophages; (2) direct cytotoxicity; (3) release of interferon. One particularly well-studied, illustrative model is ectromelia virus infection in mice,[19-22] an infection similar to smallpox in humans. Control of ectromelia virus multiplication in experimental infection begins four to six days after injection of the virus and coincides with the appearance of specific sensitized T lymphocytes. Immunity can be transferred by T lymphocytes but not by B lymphocytes, phagocytic cells, interferon or antibody. In tissue culture the sensitized T lymphocytes can directly lyse virus-infected cells, thereby destroying the intracellular environment necessary for multiplication of the virus.

In the ectromelia model, histologic preparations show that macrophages are attracted to sites of viral replication and resolution of foci of infections occurs only with the appearance of macrophages in these lesions. Elimination of either lymphocytes or macrophages allows dissemination of the virus and death of the host. Therefore, it appears that both sensitized lymphocytes and macrophages are necessary for recovery from this virus infection.

In systems in which previously sensitized T lymphocytes are able to lyse virus-infected cells, it is of interest that antibody to the virus blocks the cytotoxicity (presumably by shielding the antigen from recognition by the cytotoxic T lymphocyte).[23] Recent data indicate the existence of other mechanisms for sensitization and cytotoxicity of CMI against virus-infected cells. Nonimmune mononuclear cells (probably macrophages) lyse herpes virus-infected cells in the presence of serum with high titers of antibody against herpes virus.[24,25] In this situation, antibody may increase the cell to cell contact between macrophage and virus-infected cell. A second mechanism has been described in cells infected with lymphocytic choriomeningitis virus (LCM). The virus seems to change a normal antigen, the H-2 histocompatibility antigen, on the membrane of infected cells. This altered antigen is recognized as foreign by host lymphocytes which then lyse the infected cells.[26,27]

Cytotoxicity, or direct killing of host cells by T lymphocytes, may be beneficial, as in the ectromelia model, or may be detrimental, as illustrated by the model of LCM infection in mice.[23] In this infection, T lymphocytes are sensitized by LCM-infected cells and are then directly cytotoxic for these cells. This cytotoxicity of the lymphocytes is actually detrimental to the infected host because the cytotoxicity is directed against vital tissues—the meninges, ependyma and choroid plexus. The virus by itself does not appear to directly harm the infected tissue. Thus, viral infections may induce cytotoxicity to virus-infected host cells by an immunologic mechanism; this cytotoxicity destroys virus by destroying tissue. Benefit to the host occurs if this destructive process does not compromise function of a vital organ or tissue.

In response to infection by virus, interferon is produced by numerous cell types, including macrophages and lymphocytes.[18] This protein may bind to host ribosomes and by preventing translation of viral RNA it can prevent viral multiplication and thereby spread of virus.[28] In tissue culture, interferon decreases direct viral cytotoxicity. In animal models the levels of circulating interferon correlate with improvement in certain viral infections, and in man local interferon levels correlate with clinical recovery in humans infected with varicella-zoster.[29]

In general, cellular immunity in infections other than those caused by viruses and bacteria has been less clearly characterized. There is indirect evidence which suggests an important role for CMI in human fungal infections.[30,31] For instance, patients with underlying defects in CMI, but normal humoral immunity, such as those with chronic mucocutaneous candidiasis or Hodgkin's disease, are abnormally susceptible to disseminated fungal infections. Iatrogenic immunosuppression, which affects cellular immunity more than humoral, as in regimens administered to patients with renal or cardiac transplants, has resulted in a remarkable incidence of fungal disease. Evidence for a role for CMI derived from experimental fungal infections in animals is less convincing and consequently the relative importance of humoral immunity versus CMI has yet to be elucidated.

In protozoal infections, such as malaria and toxoplasmosis, both CMI as well as humoral antibodies may be important in overall resistance to infection caused by these organisms. In experimental malaria, manipulations which deplete thymus-dependent cells exacerbate infection; transfer of specifically immune lymphocytes con-

TABLE 5.—Congenital Disorders of Cell-Mediated Immunity

	Thymic hypoplasia (DiGeorge syndrome)	*Autosomal recessive Lymphopenia (Nezelhof syndrome)*	*Cartilage hair hypoplasia*	*Chronic mucocutaneous candidiasis*	*Immunodeficiency with thrombocytopenia (Wiskott-Aldrich syndrome)*	*Ataxia telangiectasia*	*Combined deficiency disease*
Increased incidence of infection to:							
Intracellular bacteria	...	yes	...	...	...	...	yes
Viruses	yes	yes	yes	...	yes	yes	yes
Fungi	yes	yes	...	yes	...	...	yes
Protozoa	yes	yes		...	yes	...	yes
Lymphopenia	yes	yes	yes	variable	variable	variable	yes
Absent delayed-type hypersensitivity	yes	yes	variable	variable	variable	variable	yes
Absent lymphocyte transformation to phytohemagglutinin (PHA)	yes	yes	variable	variable	variable	variable	yes
Absent lymphocyte transformation to antigen	yes	yes	yes (Varicella)	variable	variable	variable	yes

fers protection to infection in some models, but transfer of serum also confers some resistance.[32] Most likely both antibody and cells play a role in resistance to malaria (see also under Mechanisms of Cell-Mediated Immunity above).

Similarly, in murine toxoplasmosis, acquisition of resistance after infection is correlated with the appearance of specifically immune lymphocytes, activated macrophages and serum antibody.[33-35] Transfer of spleen cells specifically immune to Toxoplasma to unimmunized animals confers protection to infection.[36] Macrophages from animals chronically infected with Toxoplasma are activated and have the capacity to kill Toxoplasma, whereas macrophages from normal mice support growth of this organism.[37] Toxoplasma infection also induces humoral antibodies of both IgM and IgG classes and these contribute to protection against infection.[38]

Evidence that CMI plays an important role in other protozoal infections, such as trypanosomiasis and leishmaniasis, is beginning to accumulate,[32] but will not be discussed here.

The role of immunity in protection against most metazoan parasites is poorly understood. For instance, an intensively studied trematode parasite, Schistosoma, elicits both humoral and cellular immunity.[39] Protection against reinfection after initial exposure, however, has been consistently shown only in a few of the many animal models studied. Artificial alteration of the immunologic system of the host has no effect on development of protection.[40] Transfer of immunity to schistosomiasis either by cells or by serum has not been convincingly shown. Altering CMI prevents granuloma formation around schistosomal eggs[39] and causes more severe infection.[41,42] Other factors just beginning to be explored, such as the role of eosinophils[43] and IgE antibodies,[44] may play significant roles in schistosomiasis. In one system, however, the immunologic factors necessary for recovery from a metazoan parasite have been delineated. It has been shown that elimination of the rat nematode infection caused by Nippostrongylus brasiliensis requires both antibody and cells.[45]

Defective Functioning of Cell-Mediated Immunity

Functional impairment of CMI may result from defects in any or all elements of this arm of the immune system. This impairment may be beneficial—for example, by enabling survival of renal or cardiac transplants—or detrimental—for example, by increasing susceptibility to infection and to development of tumors. This section will briefly describe some of the major congenital and acquired defects in CMI which may lead to increased susceptibility to infection.

A number of congenital disorders of CMI and their associated laboratory abnormalities are listed in Table 5. Congenital thymic hypoplasia or DiGeorge syndrome, a classic example of a disease with defective CMI, results when the third and part of the fourth pharyngeal pouch fail to develop during embryogenesis. This failure of development results in absence of the thymus and parathyroid glands.[46] Severe hypocalcemia and tetany secondary to hypoparathyroidism occur in the neonatal period and are early clues to the diagnosis. Absence of the thymus gland prevents differentiation of lymphocyte precursors into T lymphocytes; this lack of T lymphocytes prevents expression of the normal cellular immune response. Children with this disorder are lymphopenic, and thymic dependent areas of lymph nodes show depletion of lymphocytes. Lymphocytes do not undergo transformation when exposed to either mitogen or antigen or when placed in mixed lymphocyte culture (a reaction in which lymphocytes with one type of histocompatibility antigens become sensitized to lymphocytes with different histocompatibility antigens and consequently undergo transformation). Production of lymphokines such as MIF is lacking. DH skin reactivity is absent; these patients do not react to skin testing with antigens such as streptokinase-streptodornase (SKSD) and candidin, and they cannot be sensitized with the potent artificial inducer of DH, dinitrochlorobenzene. The defects in these aspects of CMI are paralleled by a life-threatening susceptibility of these patients to pathogens such as Pneumocystis carinii, Candida albicans, herpes simplex virus and varicella-zoster virus.[46,47] They are not susceptible to organisms against which antibody and neutrophils are the primary defense mechanism. If these children survive neonatal hypocalcemia, they frequently succumb to overwhelming infection.

Other congenital diseases that effect CMI are associated with variable defects in resistance to intracellular pathogens (Table 5). One important clinical corollary in the management of patients suspected or known to have disorders of CMI is the danger associated with their receiving live vaccines such as BCG, vaccinia, measles and mumps. The attenuated organisms in these vaccines are handled easily by the immune system of normal patients but may disseminate with fatal consequences in patients with defects in CMI.

Among the acquired conditions that may cause depression of CMI function is infection itself. Those infections known to depress DH skin tests are listed in Table 6. Depression of *in vitro* lymphocyte transformation to either mitogens or antigens is associated with viral infections such as influenza and infectious mononucleosis, live vaccines such as measles-mumps-rubella and rubella, bacterial infections such as tuberculosis, leprosy, syphilis and bacterial pneumonia, and fungal infections such as coccidioidomycosis. Although most studies of depression of CMI during infections have concentrated on showing defects in DH skin testing and lymphocyte transformation to both mitogens and antigens, a recent report describes suppressed chemotaxis of monocytes from patients with acute influenza.[48] This suppression of chemotaxis persists for approximately three weeks and can be reproduced in monocytes of uninfected persons by infecting their monocytes with influenza virus. Therefore, both lymphocyte and monocyte function may be abnormal during and after acute infections. It is unclear whether depression of these *in vivo* and *in vitro* correlates of CMI by a given infection results in an increased susceptibility to other organisms. For instance, in disseminated tuberculosis and coccidioidomycosis, it is unclear whether the defect in CMI is only a manifestation of the severity of the disease or whether it also predisposes to dissemination of the infection.

An interesting example of an infection which induces immunosuppression is measles. As early

TABLE 6.—*Some Infections and Vaccines Which May Be Associated with Depressed Delayed-Type Hypersensitivity*

Viral	*Bacterial*
Measles (and vaccine)	Tuberculosis
Mumps	Leprosy
Chicken pox	Syphilis
Influenza	Streptococcal infection
Infectious mononucleosis	Brucellosis
Yellow fever	Bacterial pneumonia
Rubella vaccine	Typhoid fever
Measles-mumps-rubella vaccine	
Other	*Fungal*
Schistosomiasis	Coccidioidomycosis
Toxoplasmosis	Histoplasmosis
	Blastomycosis

as 1908 it was recognized that acute measles infection was associated with a diminution or disappearance of preexistent cutaneous DH to tuberculin.[50] These observations have been extended more recently with the demonstration of the immunosuppression which occurs following administration of live, attenuated measles vaccine. Loss of DH skin test reactivity to tuberculin, candidin and dinitrochlorobenzene for one to four weeks is observed following vaccination, and lymphocytes from these patients show depressed responsiveness to tuberculin and candidin.[51] B lymphocyte function does not appear to be depressed by measles vaccine.

There are three postulated mechanisms for the immunosuppression which follows infection with virus or vaccine. After influenza infection, either with wild virus or vaccine, there is a significant decrease in the number of circulating T lymphocytes; this may represent one mechanism of depressed lymphocyte transformation in patients with infection. In another viral infection, rubeola, *in vitro* lymphocyte transformation to unrelated antigens is notably depressed if measles virus is added to the lymphocyte culture. This appears to be due to the fact that measles virus has a predilection for infecting transforming lymphocytes (as opposed to intermitotic lymphocytes). The virus may interfere with DNA synthesis of the transforming lymphocyte and thereby suppresses lymphocyte transformation and proliferation.[52] Such a mechanism could be caused by any virus which proliferates in transforming lymphocytes. A second postulated mechanism for lack of responsiveness of CMI after measles infection is competition between the antigen of the test system (such as tuberculin) and measles virus antigen for membrane receptors on sensitized lymphocytes. When tuberculin and either measles antigen or measles virus are added to lymphocytes from tuberculin positive patients, depression of lymphocyte transformation is noted, which depends on the concentration of both antigens.[53] Therefore, three phenomena—reduction of the number of T lymphocytes, infection of transforming lymphocytes and antigenic competition—are postulated to account for the immunologic depression observed during viral infections.

These abnormalities in tests of CMI during measles infection and their possible clinical relevance have been controversial. A contested issue is whether measles predisposes to an increased incidence of primary tuberculosis or to exacerbation of active tuberculosis. In one report, a pronounced increase in the incidence of new cases of pulmonary tuberculosis was said to have occurred in an epidemic of measles in Greenland in 1951.[54] In another, the clinical course of untreated pulmonary tuberculosis in children was stated to have worsened during measles infection.[55] In contrast, a measles epidemic in a tuberculosis hospital among children with active tuberculosis was studied and no evidence for exacerbation was noted.[56]

A major class of disorders which adversely affect both humoral and cellular immunity are the malignancies. For instance, multiple myeloma, a B lymphocyte malignancy, may be associated with both profound deficiencies of normal immunoglobulins and with large concentrations of homogeneous (monoclonal) gammaglobulin or its subunits (heavy chains or light chains) or both. Hodgkin's disease, on the other hand, is an example of a malignancy of the reticuloendothelial system with adverse effects on T lymphocyte function and depression of the manifestations of CMI. In patients with Hodgkin's disease, general lymphopenia is noted which is more severe with more diffuse disease.[57] This deficiency of lymphocytes and the defect in lymphocyte function seen in this disease are clearly reflected in studies in which such patients are skin tested to a battery of specific antigens. In only 34 to 66 percent of untreated patients with Hodgkin's disease are results positive to at least one antigen whereas there is response in 100 percent of normal persons. In addition, whereas only 45 to 67 percent of the patients with Hodgkin's disease can be sensitized to dinitrochlorobenzene, 96 percent of normal people can be sensitized.[57,58] Whether the incidence of impaired DH correlates with the stage of disease is controversial. It is important to recognize that radiotherapy and chemotherapy cause profound depression of lymphocyte transformation so that evaluation of such patients after therapy has begun is of little help in determining immunologic competency and its relation to Hodgkin's disease.[59]

The abnormality in DH in patients with Hodgkin's disease is correlated with diminished *in vitro* lymphocyte transformation to antigens, mitogen and in mixed lymphocyte culture. However, there seems to be a subpopulation of patients who have depressed DH but normal *in vitro* lymphocyte transformation to PHA.[60] The depression of lymphocyte function due to Hodgkin's disease is not well understood but is attributed variously to serum factors[61-63] or to an adherent nonphagocytic mononuclear cell population.[64] Another *in vitro* measure of CMI in Hodgkin's disease, the production of the lymphokine, chemotactic factor, is normal, even when PHA responsiveness is abnormal.[65] However, levels of a naturally occurring chemotactic factor inactivator are detected in sera of patients with Hodgkin's disease, a factor which may result in a generalized defect in the ability to mobilize inflammatory cells in these patients.[66]

The abnormalities in CMI described above are associated with an increased susceptibility of patients with Hodgkin's disease to certain intracellular pathogens including herpes zoster virus, Cryptococcus neoformans,[67] Brucella,[68] Mycobacterium tuberculosis,[69] Listeria monocytogenes,[70] Salmonella[71] and Toxoplasma gondii.[72,73]

While defects in cellular immunity have been clearly established in Hodgkin's disease and certain other lymphomas, defects are less well described in other malignancies. Some advanced neoplasms such as pulmonary malignancies[74] and intracranial tumors,[75] are associated with depressed DH and mitogen-stimulated lymphocyte transformation. Failure of patients with solid tumors to be sensitized to dinitrochlorobenzene is also observed.[76] Findings in certain studies in animals show a soluble factor which is produced by tumors and which depresses macrophage-mediated resistance to infection.[77] Nonetheless, results of testing of CMI in many patients with malignancies other than those of the reticuloendothelial system who have not been immunosuppressed by cytotoxic drugs are entirely normal.[76]

Cytotoxic drugs and corticosteroids may have profound effects on both humoral and CMI response (Table 7). Defects in host defenses not associated with specific immunity may also occur; for instance, mortality rates secondary to infections in patients with acute leukemia are directly correlated with the severe neutropenia which results from these agents. Cytotoxic drugs usually affect cellular and humoral immune systems to different degrees.[78] Two chemotherapeutic drugs that are highly immunosuppressive, cyclophosphamide and methotrexate, differ both qualitatively and quantitatively in their effects on the immune system and will be used here as examples. Cyclophosphamide is a cycle-specific agent which is toxic to cells in either proliferating or resting stages but has a preferential effect on proliferating cells. Cyclophosphamide inhibits T lymphocyte proliferation as well as the production of many lymphokines.[79] It also depletes the intermitotic circulating T lymphocyte pool, thereby decreasing the number of both previously committed lymphocytes as well as those available for sensitization. Cyclophosphamide is thus able to suppress the immunologic response to a particular antigen, regardless of whether the host had been previously sensitized or not.[80] As might be expected, profound effects on antibody forming cells also occur upon exposure to this drug.

Methotrexate, on the other hand, is a phase-specific drug which acts only on dividing cells. If the drug is administered for seven days after an animal is exposed to a new antigen, depression of DH and antigen-specific lymphocyte transformation occurs. If it is administered before or after the seven day induction period, no effect on CMI function or on the number of T lymphocytes in the circulating pool is seen.[80] Therefore, methotrexate usually will not affect the CMI response to an antigen when sensitization has already been established.

Corticosteroid administration results in lymphopenia and shrinkage of organs of the reticuloendothelial system in certain animals such as mice. It has been realized, however, that there are large species differences with regard to susceptibility to corticosteroids—a fact that has generated considerable confusion in the literature. Man is relatively insensitive to corticosteroids; the principal effect of administration of the drug is to cause transient lymphopenia (24 to 48 hours).[81] In humans, this lymphopenia appears to be due to redistribution of lymphocytes of all types (T, B and null lymphocytes) to sites outside of the intravascular space and not to lysis of lymphocytes. Corticosteroids decrease expression of DH, possibly by decreasing access of lymphocytes to

TABLE 7—*Some Chemotherapeutic Agents and Their Effects on the Immune System**

Agent	*Inhibition of Primary Antibody Response*	*Inhibition of Cell-Mediated Immunity*
Cyclophosphamide	3+	3+
6-mercaptopurine	2+	2+
Methotrexate	2+	2+
Cytarabine	+	±
Vinca alkaloids	±	±
Dactinomycin	±	±
L-asparaginase	+	+
Procarbazine	2+	2+

*Adapted from Bodey et al: Postgrad Med 58:67, 1975 antigenic sites. Significant reduction of lymphocyte transformation and production of lymphokines probably does not result from administration of corticosteroids. But, interestingly, the action of certain lymphokines may be inhibited by this class of drugs; for instance, they block the effect of MIF on monocytes and macrophages.[82] Also, corticosteroids may protect the target cells from direct cytotoxicity by T cells, without directly affecting T lymphocytes themselves.[83]

Monocytopenia results from corticosteroids, presumably due to decreased release of monocytes from bone marrow and from movement of monocytes from the intravascular space. Monocytes are also adversely affected by corticosteroids, in that these agents cause a decreased clearance of particulate material and decreased bactericidal and fungicidal activity in monocytes *in vitro*.[84] Therefore, corticosteroids may affect the function of both lymphocytes and the monocyte-macrophage system in humans. Increased susceptibility to infection in animals, as well as an increased risk of reactivation of latent infections, can result from this class of drugs.[85] Although this is true also in man, this incidence will depend in large part on the underlying disease for which the corticosteroids are being administered. In general, these drugs do not increase the incidence of infection in humans significantly.[86]

Cytotoxic agents and corticosteroids are frequently administered in combination and it is the total effect of all drugs in the regimen that dictates the degree of immunosuppression. Studies with drug combinations in the treatment of malignancy in humans show there to be immunosuppression during therapy but return of immunologic competency after cessation of therapy. Continuous therapy has longer, more profound effects than does intermittent therapy.[78]

As would be expected from the above, when immunosuppressive agents are given before or simultaneously with experimental infections, DH fails to develop and mortality frequently increases. For instance, in mice, vinblastine sulfate, which irreversibly blocks cell division at metaphase, if administered 12 hours before to 24 hours after injection of Listeria, prevents development of a cellular immune response. Foci of infection which are infiltrated with macrophages in untreated mice are acellular in mice treated with vinblastine. Bacterial multiplication continues in the lesions of the latter mice without abatement and dissemination occurs.[87] Numerous other experimental infections produced by intracellular pathogens are exacerbated by immunosuppressive agents. Two examples are experimental tuberculosis in which DH is blocked and the infection is worsened by methotrexate,[88] and Candida albi-

TABLE 8—*Other Conditions Associated with Abnormalities of CMI*

Condition	*Abnormality*
Malnutrition and low birth rate in children[102-105]	Depressed DTH, LT, increased susceptibility to infection
Diabetes mellitus[106,107]	Depressed DTH, LT, granuloma formation, increased susceptibility to infection
Uremia[108,109]	Depressed DTH, LT, GVH
Age[110-113]	Depressed DTH, lymphocyte cytotoxicity, allograft rejection, MLR
Surgical operation and anesthesia[113,114]	Depressed LT, MLR, DTH, increased susceptibility to infection
Heroin addiction[115]	Depressed LT
Sarcoid[116]	Depressed DTH, LT

CMI = Cell-mediated immunity
DTH = Delayed-type hypersensitivity
LT = Lymphocyte transformation
GVH = Graft versus host
MLR = Mixed lymphocyte reaction

TABLE 9.—*Skin Test Antigens Commonly Used for Diagnosis of Infectious Diseases*

Disease or Organism	*Name of Antigen or Test*	*Time of Reaction*
Coccidioidomycosis	Coccidioidin	24-48 hr
	Spherulin	24-48 hr
Histoplasmosis*	Histoplasmin	24-48 hr
Mycobacterium tuberculosis	Purified protein derivative (PPD)	24-48 hr
Atypical mycobacteria†	PPD-A, PPD-B, PPD-G, PPD-Y	24-48 hr
Lymphogranuloma venereum	Frei test	24 hr
Mumps	Mumps antigen	24 hr

*Serology should be drawn before skin testing
†The usefulness of skin tests for diagnosis of infection with atypical mycobacteria has been questioned. Antigens are not generally available.

cans infection of mice in which corticosteroids increase mortality.[89] In humans, there is evidence for increased susceptibility to infection with the use of cytotoxic drugs. In children with acute lymphocytic leukemia, the incidence of Pneumocystis carinii pneumonitis increases when the number of cytotoxic agents used to combat the leukemia is increased.[90] Also, in patients with herpes zoster and stage III and IV lymphoma, a randomized trial suggests that treatment with cytosine arabinoside increases the time to resolution of zoster lesions. The antiviral effects of the drug are apparently less important than its immunosuppressive effects.[91]

Radiation affects proliferating and nonproliferating lymphoid cell populations and consequently depresses CMI.[92] In animals, depression of established DH and interference with initial sensitization of lymphocytes occurs as a result of radiation.[93] Susceptibility of animals to infection by such organisms as Listeria monocytogenes and Francisella tularensis is increased after exposure to continuous low dose gamma radiation.[94,95] Radiation plus agents such as cortisone and nitrogen mustard are more likely to result in relapse of latent infection than radiation or drug alone.[85] Extrapolation of these findings to humans is difficult because of the differences in radiation doses given to humans and to experimental animals and because of the deficiencies in CMI secondary to the underlying disease process in humans for which the radiation is being administered.[96]

Other drugs are associated with abnormalities of *in vitro* and *in vivo* functions of CMI including rifampicin[97,98] and niridazole, an antischistosomal drug.[99,100] The relevance of these abnormal CMI functions to susceptibility to infection is unknown at this time.

Antilymphocyte serum, which has proved useful in prolonging allograft transplants, destroys lymphocytes in the circulating pool leading to lymphopenia and abnormalities in the function of CMI.

In addition to those discussed, leukocytosis, anemia and fever depress DH skin responses.[101] A variety of other conditions are associated with abnormalities of CMI, some of which are listed in Table 8.

Diagnostic and Clinical Considerations

Delayed hypersensitivity skin tests which measure the response of a host to antigens of a particular pathogen can be useful in diagnosis of infectious diseases (Table 9). Absence of skin reactivity to these antigens may indicate either lack of previous exposure to the antigen, defect(s) of CMI, failure to properly inject the antigen intradermally or a defect in the ability of the host to develop nonspecific inflammatory skin responses (this latter defect can be tested by placing irritating substances such as benzalkonium chloride on the skin).

A brief outline of important considerations in the evaluation of patients with suspected defects in CMI is given in Table 10. Tests of the overall function of CMI include DH skin tests to antigens against which most people are sensitized, such as streptokinase-streptodornase (SKSD), mumps antigen, candidin and trichophyton. Almost 100 percent of normal adults will respond to at least one of these antigens. If these fail to elicit a response, sensitization of the patient may be attempted with a chemical such as dinitrochlorobenzene;[118] successful sensitization with this agent represents the ability of the CMI system to respond to new antigens. If there is no response to these tests, the patient may have a significant defect in CMI. For any skin testing, an initial evaluation should be

TABLE 10.—*Evaluation of Cell-Mediated Immunity**

History
- Increased frequency and severity of infections
- Abnormal response to live vaccines (e.g. Vaccinia)
- Frequent infections with less common pathogens (e.g. fungi)
- Recurrent diarrhea
- Family history of increased susceptibility to infection

Physical Examination
- Signs of chronic infection
- Absence of lymphoid tissue
- Signs associated with specific immunodeficiency disorders (see Table 5)

Laboratory
- Peripheral blood lymphocyte count (should be greater than 1200/cu mm) and morphology (presence of small lymphocytes [T lymphocytes])
- Cutaneous delayed hypersensitivity response to antigens (mumps, Candida, PPD, SKSD) and dinitrochlorobenzene (DNCB)
- Quantitation of T lymphocytes (e.g. sheep red blood cell rosetting)
- Chest x-ray for presence of thymic shadow in children
- Response of lymphocytes in vitro to mitogens, specific antigens, and allogeneic cells
- Lymphokine production (e.g. MIF)
- Lymph node biopsy
- Rejection of allogeneic graft

PPD = purified protein derivative
SKSD = streptokinase-streptodornase
MIF = migration inhibition factor

*Adapted after Gelfand et al[117]

made at two to six hours after injection of antigen for immediate hypersensitivity reactions which are not CMI responses and may result in false positive readings 24 to 48 hours later.

In vitro tests of CMI function are usually carried out only by specialized laboratories. Tests which may provide information regarding a specific defect of CMI in immunodeficient patients include quantitation of T and B lymphocytes in peripheral blood, ability of blood lymphocytes to undergo transformation to mitogens or specific antigens (such as SKSD) and production of lymphokines such as MIF. In certain conditions associated with a defect in CMI, there may be a dichotomy between the DH response *in vivo* and results of *in vitro* correlates of DH (for example, mucocutaneous candidiasis).

Enhancement of CMI in order to increase resistance to pathogenic microorganisms has been attempted, but success has been limited. Some of the more promising agents with potential for enhancing nonspecifically the immunologic response of a host and thereby increasing resistance to or combating already existing infection are discussed below. Corynebacterium parvum (killed) and BCG (live or various extracts) appear to stimulate both afferent and efferent limbs of CMI. The effect of these adjuvants may result from the stimulatory effect they have on macrophages. The function of macrophages in both the afferent limb (Figure 1) and the efferent limb (Figure 3) of the immune response are enhanced by these adjuvants. Adjuvants produce significant protection against certain infections in experimental animals,[119] but similar studies in humans have not been conducted.

Transfer factor is a relatively small molecule found in circulating human leukocytes that can transfer to nonimmunized persons the pattern of DH and presumably the immunologic competence of the donor. This effect may last for weeks or even years. Restoration of both DH and of the production of lymphokines, as well as clearing of chronic infections, occurs in some patients with congenital immunologic deficiencies, such as Wiscott-Aldrich syndrome[120] and chronic mucocutaneous candidiasis.[121] Transfer factor has been tried in numerous patients with a variety of infectious diseases (coccidioidomycosis, for instance) in an uncontrolled manner; conclusions regarding this form of therapy in infectious diseases must be reserved until properly controlled studies are carried out.[122]

Levamisole is an antihelminthic drug that also enhances CMI *in vitro* and *in vivo*. Levamisole restores responsiveness to dinitrochlorobenzene in anergic patients with malignancies[123] and restores responsiveness to tuberculin in elderly patients with depressed DH to this antigen.[124] The drug also enhances lymphocyte transformation to specific antigens in certain situations. Whether levamisole enhances macrophage functions such as phagocytosis *in vitro* and *in vivo* is controversial.[125,126]

There is evidence from a double-blind controlled trial in children with recurrent upper respiratory tract infections that levamisole treatment significantly reduces the number, duration and severity of infections compared with placebo.[127] Uncontrolled trials indicate that the drug may be useful in patients with recurrent aphthous stomatitis and recurrent herpes simplex infections.[128,129] More controlled clinical trials are needed to definitively determine the effectiveness of this drug to the above infections, as well as to other infections.[130]

Interferon, which was discussed above under the section on Evidence for the Role of CMI in Resistance to Infections, appears efficacious in certain viral infections. High doses of interferon given to humans experimentally exposed to rhinovirus 4 (a common cause of upper respiratory tract infection) prevents symptoms of infection and virus shedding.[131] However, interferon must be given one day before and continued for three days after challenge with rhinovirus to produce the protective effect. In addition, the high doses necessary to produce this effect are currently prohibitively expensive. Human leukocyte interferon given to patients with chronic hepatitis B and chronic active hepatitis causes Dane particles, which most likely represent complete hepatitis B virus, to disappear from the blood.[132] Repeated administration results in disappearance of the Dane particle for prolonged periods. Interferon has also been used in the treatment of herpetic keratitis[133,134] and cytomegalovirus infections[135,136] but without evidence of efficacy. Other trials of the use of interferon in viral infections are currently in progress.[137] Inducers of interferon have also been used in man. Preliminary clinical trials indicate that these agents may prevent or reduce rhinovirus infections.[138]

The thymus gland and its products appear to play an important role in establishing immunocompetence and possibly in regulation of CMI.[139]

Thymus gland transplants in selected patients with DiGeorge syndrome successfully restore immunocompetence.[140-142] In addition, a variety of cell-free extracts of thymus gland have the ability to restore immunocompetence to neonatally thymectomized animals and to accelerate maturation of CMI.[139] Thymosin, a product of the thymus gland which has been detected in the peripheral circulation, is a protein with a molecular weight of 12,200 and a known amino acid sequence. This thymic product enhances lymphocytopoiesis, restores immunologic competence in certain situations and enhances expression of T lymphocyte function *in vitro* and *in vivo*.[49,139,143]. The potential for the use of thymosin in treating both congenital and acquired deficiencies in CMI appears great, although controlled trials have not been carried out. Continued support for research in this area is critical if we are to seek to prevent or control infection in the immunosuppressed host.

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Diet and Diabetes

. . . Greater emphasis should be put on diet as a first treatment for maturity onset diabetes. After all, this was always the basis of therapy for diabetes. Before insulin came into effect 55 years ago, diet was the only thing that we had, and we must go back to diet.

—STANLEY N. COHEN, MD, *Philadelphia*
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